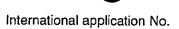
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1152WOORD01				FOR FURTHER A	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)					
International application No. PCT/EP 03/13604				International filing date 03.12.2003	(day/mont	h/year)	Priority date (day/month/year) 06.12.2002			
	rnation 7D40		ent Classification (IPC) or bo	th national classification	and IPC					
1	Applicant ALTANA PHARMA AG									
1.	<ol> <li>This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</li> </ol>									
2.	This REPORT consists of a total of 6 sheets, including this cover sheet.									
	This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).									
	The		nexes consist of a total of		ave msau	ctions under tr	ie PC1).			
3.	This		t contains indications rela	ating to the following it	ems:					
	1		Basis of the opinion							
	11		Priority							
	III				ovelty, in	ventive step ar	nd industrial applicability			
	IV		Lack of unity of inventio							
	V	⊠	citations and explanatio	ns supporting such sta	ith regard atement	to novelty, inve	entive step or industrial applicability;			
	VI		Certain documents cited	-						
	VIII		Certain defects in the in	* *						
•	VIII		Certain observations on	the international appl	ication .	•				
Date of submission of the demand Date of					Date of c	ompletion of this	report			
11.0	11.06.2004					22.12.2004				
	Name and mailing address of the international preliminary examining authority:				Authorize	ed Officer	Wither Poisons,			
	<u>)</u> ))	D-10 Tel.	opean Patent Office - Gitsch 0958 Berlin +49 30 25901 - 0 : +49 30 25901 - 840	iner Str. 103	Hass, C	e No. +49 30 25	901-340			
					···					



PCT/EP 03/13604

l	В	asi	s	of	the	e re	as	OI	rt

1.	With regard to the <b>elements</b> of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):							
	De	scription, Pages						
	1-1	0	as originally filed					
	Cla	ims, Numbers						
		•						
	1-2	U	as originally filed					
	Wit lang	With regard to the <b>language</b> , all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.						
	The	ese elements were av	ailable or furnished to this Authority in the following language: , which is:					
		the language of a tra	anslation furnished for the purposes of the international search (under Rule 23.1(b)).					
		the language of publ	ication of the international application (under Rule 48.3(b)).					
		the language of a tra Rule 55.2 and/or 55.	anslation furnished for the purposes of international preliminary examination (under 3).					
3.	Witl inte	h regard to any <b>nucle</b> rnational preliminary	otide and/or amino acid sequence disclosed in the international application, the examination was carried out on the basis of the sequence listing:					
		contained in the inte	rnational application in written form.					
		filed together with the international application in computer readable form.						
		furnished subsequently to this Authority in written form.						
		furnished subsequently to this Authority in computer readable form.						
		The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.						
		The statement that the listing has been furnit	ne information recorded in computer readable form is identical to the written sequence ished.					
4.	The	amendments have re	esulted in the cancellation of:					
	□ ·	the description,	pages:					
		the claims,	Nos.:					
		the drawings,	sheets:					
5.		This report has been been considered to g	established as if (some of) the amendments had not been made, since they have to beyond the disclosure as filed (Rule 70.2(c)).					
		(Any replacement sh report.)	eet containing such amendments must be referred to under item 1 and annexed to this					

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6. Additional observations, if necessary:

- V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- 1. Statement

Novelty (N)

Yes: Claims

1-19

No:

Claims

Claims

Claims

20

Inventive step (IS)

Yes: Claims

7-9, 16-19

No:

1-6, 10-15, 20

Industrial applicability (IA)

Yes: No:

Yes: Claims

1-20

2. Citations and explanations

see separate sheet

#### Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

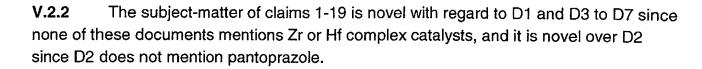
#### V.1 Cited documents

- D1: WO 96/02535 A (COTTON HANNA KRISTINA; LARSSON ERIK MAGNUS (SE); ASTRA AB (SE); SOERE) 1 February 1996 (1996-02-01)
- D2: BONCHIO M ET AL: "The first Chiral Zirconium(IV) catalyst for highly stereoselective sulfoxidation" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 64, no. 4, 1999, pages 1326-1330, XP002242676 ISSN: 0022-3263
- D3: WO 92/08716 A (BYK GULDEN LOMBERG CHEM FAB) 29 May 1992 (1992-05-29)
- D4: WO 94/24867 A (SEPRACOR INC) 10 November 1994 (1994-11-10)
- D5: WO 94/25028 A (SEPRACOR INC) 10 November 1994 (1994-11-10)
- D6: WO 99/47514 A (KNOLL AG; BRENNAN JAMES PATRICK (GB); TURNER ANDREW TIMOTHY (GB)) 23 September 1999 (1999-09-23)
- D7: WO 96/17076 A (ASTRA AB; HOLT ROBERT (GB); LINDBERG PER (SE); REEVE CHRISTOPHER (GB)) 6 June 1996 (1996-06-06)

### V.2 Novelty

V.2.1 D1 and D3 destroy the novelty of the subject-matter of claim 20; in D1, (S)-pantoprazole (the (-)-form) is even disclosed in defined enentiomeric purity. Claim 20 should thus be deleted. Note: The formulation of claim 20 as product-by-process claim does not render the claimed product novel since normally it cannot be detected in a product how it was made. Claims for products defined in terms of processes for their preparation are admissible only if the products themselves are novel and inventive (and industrially applicable) and if there is no other information available in the application which could enable the applicant to define the product satisfactorily by reference to its composition, structure or some other testable parameter(s). In the present case, the compound can be readily defined by its chemical structure and by stereochemical parameters.

Form PCT/Separate Sheet/409 (Sheet 1) (EPO-April 1997)



#### V.3 Inventive step

- **V.3.1** According to the description, the problem underlying the present application is to provide a further process for the preparation of (S)-pantoprazole.
- V.3.2 The subject-matter of claim 20 is not novel (see above). For claims 1-19, the closest prior art with regard to the preparation of (S)-pantoprazole is D1. This document discloses a process as defined above, comprising the sulfoxidation of an intermediate having a methylthio group to (S)-pantoprazole (which has a methylsulfinyl group), however, in D1, a titanium compound is used instead of the zirconium compound according to the present application. The following optional features, which are comprised by the present claims, are also disclosed in D1: The use of cumene hydroperoxide, the presence of an organic base (which is a tertiary amine), the use of an organic solvent optionally containing water (see D1, example 23); the organic solvent can be methyl isobutyl ketone (D1, page 15, lines 13 and 14). Furthermore, D2 is relevant prior art as to the use of a chiral zirconium complex for stereoselective sulfoxidation. In D2, chiral zirconium complexes, especially zirconium(IV) catalysts are discussed as an alternative to titanium(IV) catalysts for stereoselective sulfoxidation reactions.

# V.3.3 Inventive step evaluation with regard to the zirconium catalyst:

- V.3.3.1 With the knowledge of D2, the skilled person, faced with the problem defined in point V.3.1, would be encouraged to replace titanium by zirconium also in connection with the preparation of (S)-pantoprazole. So the subject-matter of claims 1 and 2 (as to the embodiment comprising the Zr complex) is to be considered, in view of the combined teachings of D1 and D2, as an obvious result from the prior art. In view of D1 and D2, claims 3 to 6 and 10 to 15 do not add subject-matter which could be regarded as non-obvious (see also point V.3.2). Consequently, claims 1 to 6 and 10 to 15 do not involve an inventive step.
- **V.3.3.2** Inventive step could be acknowledged for the subject-matter of claims 7 to 9 and 16 to 19 since it could not be expected that, if Ti is replaced with Zr, a (+)-L-tartaric acid derivative instead of a (-)-L-tartaric acid derivative can be used as chiral auxiliary

reagent (the applicant submits that (+)-L-tartaric acid derivatives are easier available with respect to their more frequent natural occurrence).

## V.3.4 Inventive step evaluation with regard to the <u>hafnium</u> catalyst:

Hafnium catalysts in connection with stereoselective sulfoxidation reactions are not known from any of the cited prior art documents. The use of hafnium complex catalyst in the preparation of (S)-pantoprazole is thus non-obvious for a skilled person. Therefore, with regard to the use of hafnium in the claimed process, claims 1, 3 to 5 and 7 to 15 could be considered to involve an inventive step (the remaining claims 2, 6 and 16 to 19 refer to Zr only).

- V.3.5 From the foregoing evaluation it is evident that the inventive concept providing said process by making use of a Zr complex is different from the inventive concept providing said process by making use of an Hf complex: In case of the chiral Zr complex inventive step is based on the finding that (+)-L-tartaric acid derivatives instead of (-)-L-tartaric acid derivatives can be used; in case of the chiral Hf complex inventive step is based on the fact that apparently no Hf complex hitherto has been used for sulfoxidation reactions at all. The applicant is thus informed that there is a lack of unity (within the meaning of Rule 13(1) PCT) between the subject-matter of the claims referring to Zr complexes on the one hand and subject-matter of the claims referring to Hf complexes on the other hand. However, a complete search was executed for the subject-matter of the claims, and also an international preliminary examination was carried out for the complete subject-matter of the claims on file.
- **V.3.6** Claim 1 should have been restricted to such subject-matter which can be expected to actually solve the problem underlying the present application. Because of the very examples disclosed in the description it must be assumed that for carrying out the invention(s) the presence of a (+)-L-tartaric acid derivative is essential. The subject-matter of claim 7 therefore should have been introduced into claim 1 and 2 as an essential feature.

## V.4 Industrial applicability

The subject-matter of claims 1-20 is industrially applicable.